

AMENDMENTS TO THE CLAIMS

1-5. **(Canceled)**

6. **(Previously Presented)** The recombinant inhibitor protein, or inhibiting fragment thereof, which inhibits a kallikrein, of claim 39, wherein the kallikrein is hK2 kallikrein.

7-16. **(Canceled)**

17. **(Currently Amended)** A pharmaceutical composition comprising the recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39 ~~or 40~~, and a pharmaceutically acceptable carrier.

18-27. **(Canceled)**

28. **(Currently Amended)** A method for producing the recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39, comprising

- a) selecting a polynucleotidic sequence encoding ~~[[a]]~~ the modified Reactive Serpin Loop (RSL) which inhibits ~~[[said]]~~ the Kallikrein by phage displayed library screening;
- b) introducing ~~[[said]]~~ the polynucleotidic sequence into a sequence encoding ~~[[a]]~~ the α -1 antichymotrypsin (ACT) serpin, so as to obtain ~~[[a]]~~ the recombinant inhibitor protein;
- c) allowing expression of ~~[[said]]~~ the recombinant inhibitor protein in a cell expression system under suitable conditions; and
- d) recovering ~~[[said]]~~ the recombinant inhibitor protein.

29. **(Canceled)**

30. **(Previously Presented)** The method of claim 28, wherein the suitable conditions comprise culturing the cell expression system at a temperature between 10-40°C during 10-30 hours.

31. **(Previously Presented)** The method of claim 30, wherein the suitable conditions comprise a temperature of 16°C during 16 hours.

32. **(Previously Presented)** The method of claim 28, wherein step d) is achieved by separation after extraction of the recombinant inhibitor protein, or inhibiting fragment thereof, from the cell expression system.

33. **(Previously Presented)** The method of claim 32, wherein the separation of the recombinant inhibitor protein, or inhibiting fragment thereof, is achieved by affinity chromatography.

34-35. **(Canceled)**

36. **(Previously Presented)** The method of claim 28, wherein the cell expression system is a bacterial cell.

37. **(Canceled)**

38. **(Previously Presented)** A diagnostic kit for the detection of a kallikrein in a specimen comprising the recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39.

39. **(Currently Amended)** A recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits a kallikrein, comprising ~~[[a]]~~ an α -1 antichymotrypsin (ACT) serpin sequence with a modified Reactive Serpin Loop (RSL) having an amino acid ~~substitutions~~ substituted sequence within the P6-P'6 interval, which result in

increased binding affinity for the kallikrein, wherein ~~at least one of the amino acid~~
substitutions ~~replaces~~ at P1 ~~[[with]]~~ is an arginine (R) ~~or a lysine (K)~~ and creates a
substituted P1-P'1 scissile bond wherein the recombinant inhibitor protein, or an
inhibiting fragment thereof, comprises the amino acid substituted sequence within the P6-
P'6 interval selected from the group consisting of
the P3-P'2 pentapeptide SSRTE (SEQ ID NO:23),
the P3-P'2 pentapeptide KTRSN (SEQ ID NO:24),
the P4-P'1 pentapeptide ISPRS (SEQ ID NO:25),
the P4-P'1 pentapeptide GVFRS (SEQ ID NO:26),
the P4-P'1 pentapeptide GTVRS (SEQ ID NO:27),
the P4-P'1 pentapeptide ETKRS (SEQ ID NO:28),
the P3-P'2 pentapeptide LGRSL (SEQ ID NO:29),
the P3-P'2 pentapeptide RGRSE (SEQ ID NO:30),
the P2-P'3 pentapeptide RRSID (SEQ ID NO:31),
the P3-P'2 pentapeptide VLRSP (SEQ ID NO:32),
the P3-P'2 pentapeptide PFRSS (SEQ ID NO:33),
the P1-P'4 pentapeptide RSGSV (SEQ ID NO:34),
the P4-P'1 pentapeptide ARARS (SEQ ID NO:35),
the P3-P'2 pentapeptide SDRTA (SEQ ID NO:36),
the P3-P'2 pentapeptide KLRTT (SEQ ID NO:37),
the P1-P'4 pentapeptide RAAMM (SEQ ID NO:38),
the P2-P'3 pentapeptide TRAPM (SEQ ID NO:39),
the P3-P'2 pentapeptide DVRAA (SEQ ID NO:40),
the P3-P'2 pentapeptide PGRAP (SEQ ID NO:41),
the P4-P'1 pentapeptide VESRA (SEQ ID NO:42),
the P2-P'3 pentapeptide ARASE (SEQ ID NO:43),
the P4-P'1 pentapeptide TLQRV (SEQ ID NO:44),
the P4-P'1 pentapeptide RLERV (SEQ ID NO:45),
the P2-P'3 pentapeptide ERVSP (SEQ ID NO:46),
the P4-P'1 pentapeptide SSPRV (SEQ ID NO:47),

the P1-P'4 pentapeptide RVGPY (SEQ ID NO:48),
the P4-P'1 pentapeptide PSARM (SEQ ID NO:49),
the P3-P'2 pentapeptide RGRMA (SEQ ID NO:50),
the P3-P'2 pentapeptide TVRMP (SEQ ID NO:51),
the P2-P'3 pentapeptide LRMPT (SEQ ID NO:52),
the P2-P'3 pentapeptide HRMSS (SEQ ID NO:53),
the P1-P'4 pentapeptide RPQEL (SEQ ID NO:54),
the P2-P'3 pentapeptide VRPLE (SEQ ID NO:55),
the P3-P'2 pentapeptide SGRLA (SEQ ID NO:56),
the P4-P'1 pentapeptide GTLRF (SEQ ID NO:57),
the P3-P'2 pentapeptide QWRNS (SEQ ID NO:58),
the P1-P'4 pentapeptide RNDKL (SEQ ID NO:59),
the P2-P'3 pentapeptide MRNRA (SEQ ID NO:60),
the P2-P'3 pentapeptide TRDSR (SEQ ID NO:61),
the P4-P'1 pentapeptide TGSRD (SEQ ID NO:62), and
the P4-P'1 pentapeptide IMSRQ (SEQ ID NO:63).

40. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[63]] 39, wherein the ~~kalikrein is kalikrein hK2~~ modified RSL having amino acid substitutions is selected from the group consisting of amino acids 367 to 378 of SEQ ID NO:6 and SEQ ID NO:12.

41. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39, wherein the amino acid ~~substitutions are~~ substituted sequence within the P6-P'6 interval is selected from the group consisting of
the RSL of MD820 (SEQ ID NO: 16),
the RSL of ACT62 (SEQ ID NO:17),
the RSL of MD83 (SEQ ID NO:18),
the RSL of MD67 (SEQ ID NO:19),
the RSL of MD61 (SEQ ID NO:20),
the RSL of MD518 (SEQ ID NO:21), and

the RSL of MDCI (SEQ ID NO:22).

42. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[63]] 39, wherein the pentapeptide is a substrate peptide selected by said kallikrein using a phage-displayed random pentapeptide library.

43-50. **(Canceled)**

51. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[65]] 39, wherein the amino acid substituted sequence within the P6-P'6 interval is a P3-P'2 ~~comprises an~~ amino acid sequence selected from the group consisting of

SSRTE (SEQ ID NO:23),

KTRSN (SEQ ID NO:24),

LGRSL (SEQ ID NO:29),

RGRSE (SEQ ID NO:30),

VLRSP (SEQ ID NO:32),

PFRSS (SEQ ID NO:33),

SDRTA (SEQ ID NO:36),

KLRTT (SEQ ID NO:37),

DVRAA (SEQ ID NO:40),

PGRAP (SEQ ID NO:41),

RGRMA (SEQ ID NO:50),

TVRMP (SEQ ID NO:51),

SGRLA (SEQ ID NO:56), and

QWRNS (SEQ ID NO:58), and

~~SEQ ID NO:67.~~

52. **(Canceled)**

53. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[65]] 39, wherein the amino acid substituted sequence within the P6-P'6 interval is a P4-P'1 ~~comprises an amino acid~~ sequence selected from the group consisting of

ISPRS (SEQ ID NO:25),
GVFRS (SEQ ID NO:26),
GTVRS (SEQ ID NO:27),
ETKRS (SEQ ID NO:28),
ARARS (SEQ ID NO:35),
VESRA (SEQ ID NO:42),
TLQRV (SEQ ID NO:44),
RLERV (SEQ ID NO:45),
SSPRV (SEQ ID NO:47),
PSARM (SEQ ID NO:49),
GTLRF (SEQ ID NO:57),
TGSRD (SEQ ID NO:62),
IMSRQ (SEQ ID NO:63), and
PFRKI (SEQ ID NO: 66).

54. **(Canceled)**

55. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[65]] 39, wherein the amino acid substituted sequence within the P6-P'6 interval is a P2-P'3 ~~comprises an amino acid~~ sequence selected from the group consisting of

RRSID (SEQ ID NO:31),
ARASE (SEQ ID NO:43),
ERVSP (SEQ ID NO:46),
LRMPT (SEQ ID NO:52),
HRMSS (SEQ ID NO:53),

VRPLE (SEQ ID NO:55),
MRNRA (SEQ ID NO:60),
TRDSR (SEQ ID NO:61), and
LRSRA (SEQ ID NO: 68).

56. (Canceled)

57. (Currently Amended) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[65]] 39, wherein the amino acid substituted sequence within the P6-P'6 interval is a P1-P'4 ~~comprises an amino acid~~ sequence selected from the group consisting of

RSGSV (SEQ ID NO:34),
RAAMM (SEQ ID NO:38),
RVGPY (SEQ ID NO:48),
RPQEL (SEQ ID NO:54), and
RNDKL (SEQ ID NO: 59).

58-67. (Canceled)

68. (Currently Amended) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39 or 40, ~~wherein the amino acid substitutions are modified by further~~ comprising at least one additional substrate active site sequence modification.

69. (Currently Amended) The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[65]] 39, ~~wherein the substituted pentapeptide sequences are modified by further~~ comprising at least one additional substrate active site sequence modification.

70. (New) A method for identifying a recombinant inhibitor protein comprising a modified Reactive Serpin Loop, or inhibiting fragment thereof, which inhibits a Kallikrein, comprising

- a) selecting a polynucleotidic sequence encoding the modified Reactive Serpin Loop (RSL) which inhibits the Kallikrein by phage displayed library screening;
- b) introducing the polynucleotidic sequence into a sequence encoding the α -1 antichymotrypsin (ACT) serpin, so as to obtain the recombinant inhibitor protein;
- c) allowing expression of the recombinant inhibitor protein in a cell expression system under suitable conditions;
- d) recovering the recombinant inhibitor protein; and
- e) assaying the recombinant inhibitor protein for its ability to inhibit the activity of the kallikrein.

71. **(New)** The method of claim 70, wherein the suitable conditions comprise culturing the cell expression system at a temperature between 10-40°C during 10-30 hours.

72. **(New)** The method of claim 71, wherein the suitable conditions comprise a temperature of 16°C during 16 hours.

73. **(New)** The method of claim 70, wherein step d) is achieved by separation after extraction of the recombinant inhibitor protein, or inhibiting fragment thereof, from the cell expression system.

74. **(New)** The method of claim 32, wherein the separation of the recombinant inhibitor protein, or inhibiting fragment thereof, is achieved by affinity chromatography.

75. **(New)** The method of claim 28, wherein the cell expression system is a bacterial cell.

76. **(New)** The method of claim 28, wherein the fragment is at least 40% of the length of the native ACT amino acid sequence.

77. **(New)** The method of claim 28, wherein the fragment is at least 70% of the length of the native ACT amino acid sequence.

78. **(New)** The method of claim 28, wherein the fragment is at least 80% of the length of the native ACT amino acid sequence

79. **(New)** The method of claim 28, wherein the fragment is at least 90% of the length of the native ACT amino acid sequence.